Strength of Molecular Complexation of Apolar Solutes in Water and in Organic Solvents Is Predictable by Linear Free Energy Relationships: A General Model for Solvation Effects on Apolar Binding

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Abstract: The stability of an inclusion complex formed by a macrobicyclic cyclophane host and pyrene was studied in water and 17 organic solvents covering the entire polarity range. Complexation strength decreases steadily for the series of solvents beginning with water ($-\Delta G°$ = 9.4 kcal·mol^{-1} at T = 303 K) and continuing to nonaqueous polar protic solvents, to dipolar aprotic solvents, and finally to apolar solvents, e.g, carbon disulfide ($-\Delta G°$ = 1.3 kcal·mol^{-1}). This large difference in binding strength results from solvation effects. The empirical solvent polarity parameter $E_T(30)$ is very useful for predicting and rationalizing, in terms of a linear free energy relationship, the strength of apolar host–guest complexation in different solvents. While the most stable complexes form in water, strong binding is also observed in formamide and in small alcohols. The free energy of complexation in 2,2,2-trifluoroethanol is measured as $-\Delta G°$ = 7.8 kcal·mol^{-1}, and this solvent comes closest to water in its ability to promote apolar binding processes. A general model of solvation effects on apolar complexation is presented. Binding is strongest in solvents with low molecular polarizability and with high cohesive interactions. The most stable complexes of apolar substrates form in water since solvent cohesive interactions are very large and water molecules possess the lowest molecular polarizability of all solvent molecules. The role of water in apolar complexation processes can be rationalized completely on the basis of its physical properties.

Cyclophanes with deep enforced cavities provide suitable model systems for the hydrophobic binding sites where enzymes and antibodies bind aromatic substrates.[1-12] Many of the highly structured, stable complexes formed between these synthetic macrocyclic receptors and apolar aromatic molecules in water approach the level of enzyme–substrate complexes in their stability and specificity. In recent years, cyclophane complexation of apolar arenes has also been observed in organic solvents.[2,13,14] From comparative binding studies, it is evident that the stability of a complex is considerably reduced in organic solvents as compared to water even if the supramolecular geometries and, hence, the host–guest interactions are very similar in the aqueous and in the nonaqueous environment. Special driving forces for complexation, entropic[15] and enthalpic[16,17] hydrophobic effects, have been advanced to explain the increased stability of apolar host–guest complexes in aqueous solutions.

Water is the essential biological fluid which promotes aggregation and complexation processes necessary to sustain all functions of life. We address the fundamental question of whether the apolar complexation promoting characteristics of water can be correlated with such characteristics of other solvents and are predictable solely on the basis of physical constants and properties.[18] Insight into this question is obtained by evaluating comparative binding studies in water and a large variety of organic solvents with a linear free energy relationship. For the tight complexation of neutral aromatic substrates at shape-complementary apolar binding sites, we show that water does not exhibit an unusual behavior in promoting complexation and that some solvents approach water in their ability to assist apolar binding. Our studies show that the magnitude of the apolar binding strength is predictable in all solvents including water. A general model to explain the origins of the solvent dependency of apolar complexation is presented.

A Macrobicyclic Host and Its Pyrene Complex Meet the Requirements for Comprehensive Comparative Binding Studies in Aqueous and Organic Solvents

To compare apolar binding strength in aqueous and organic solutions, we chose pyrene complex **1** of a macrobicyclic cyclophane host for the following reasons:

(i) The host and its pyrene complex are soluble in solvents covering the entire polarity range from water to apolar solvents. In some studies, dimethyl sulfoxide (1 or 10% v/v) was added as a cosolvent to increase the solubility of free pyrene.

(ii) According to extensive ^{1}H NMR studies,[13] pyrene complex **1** adopts a very similar geometry in all solvents. For steric reasons, pyrene can only be incorporated in the cyclophane plane passing

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Table I. Association Constants K_a and Free Energies of Formation $-\Delta G°$ of Complex **1** in 18 Solvents of Different Polarity As Expressed by $E_T(30)$ Values, T = 303 K

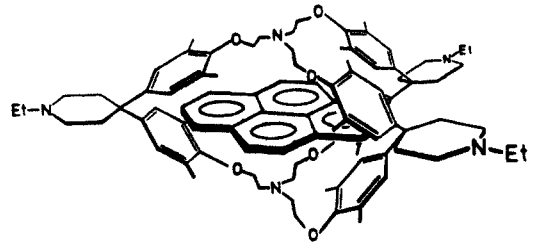
run	solvent	K_a (L·mol^{-1})	$-\Delta G°$ (kcal·mol^{-1})[a]	$E_T(30)$ (kcal·mol^{-1})
1	water/1% Me_2SO[b]	6.0×10^6	9.4	63.0
2	2,2,2-trifluoroethanol/1% Me_2SO	4.2×10^5	7.8	59.4
3	ethylene glycol/10% Me_2SO	1.8×10^5	7.3	55.9
4	methanol	4.4×10^4	6.4	55.5
5	formamide/10% Me_2SO	3.0×10^4	6.2	55.2
6	ethanol	2.5×10^4	6.1	51.9
7	*N*-methylacetamide/10% Me_2SO	1.5×10^4	5.8	52.1
8	*N*-methylformamide/10% Me_2SO	4.8×10^3	5.1	54.0
9	acetone	1.2×10^3	4.3	42.2
10	*N*,*N*-dimethylacetamide/10% Me_2SO-d_6	1.1×10^3	4.2	43.0
11	dimethyl sulfoxide-d_6[c]	6.9×10^2	3.9	45.0
12	*N*,*N*-dimethylformamide-d_7/10% Me_2SO-d_6	1.6×10^2	3.0	43.7
13	*N*,*N*-dimethylformamide-d_7	1.5×10^2	2.9	43.8
14	dichloromethane-d_2	1.2×10^2	2.9	41.4
15	tetrahydrofuran-d_8	8.4×10^1	2.7	37.4
16	chloroform-d_1	4.3×10^1	2.3	39.1
17	benzene-d_6	1.2×10^1	1.5	34.5
18	carbon disulfide	9×10^0	1.3	32.6

[a] Errors in $\Delta G°$: ±0.1 kcal·mol^{-1} in runs 1–10, 12, and 14; ±0.2 kcal·mol^{-1} in runs 11, 13, and 15–18.[13] [b] The aqueous solution contains a [Na_2CO_3] = 10^{-3} mol·L^{-1} to prevent protonation of the pentaamine host. [c] H/D solvent isotope effects are below the error in K_a.

through the three spiro carbon atoms. In ^{1}H NMR titrations, similar complexation shifts at saturation binding are observed for both host and guest resonances in various solvents.

(iii) Even in apolar solvents, the stability of the pyrene complex is sufficient for a meaningful evaluation of complexation strength. Stable cyclophane complexes of apolar benzene and naphthalene derivatives have only been formed in water, in alcohols, and in dimethyl sulfoxide.[16,19]

(iv) Because all solvent molecules in Table I are small enough to easily enter and exit the large, highly preorganized host cavity without causing major conformational strain, the host cavity is completely solvated when pyrene is not bound. This complete solvation of the host cavity by all solvents is an important criterion for a meaningful comparative study. Comparison would not be meaningful if differences in binding strength would result from the fact that one solvent molecule solvates the binding site whereas a second, larger solvent molecule does not fit and leaves a non-solvated, empty cavity. Furthermore, conditions were chosen to ensure that no protonation of the nitrogen atoms in the host occurred in any solvent.



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Stability of Complex 1 in Water and in Organic Solvents

Table I shows the stability constants, K_a (L·mol^{-1}), and free energies of formation, $-\Delta G°$ (kcal·mol^{-1}), of complex **1** in 18 solvents at T = 303 K as well as the empirical solvent polarity parameter $E_T(30)$ (kcal·mol^{-1})[20a] measured for these solvents. In previous work,[13] nine of the binding numbers of Table I were obtained and correlated with $E_T(30)$ values.[2] This correlation served as a useful guideline for choosing appropriate host and guest concentrations for those titrations that provided the new data presented in this paper. Association constants below $K_a \approx 5 \times 10^3$ L·mol^{-1} were determined by ^{1}H NMR titrations; all higher association constants were obtained by fluorescence titrations. The titrations were evaluated with a nonlinear least-squares curve fitting procedure. To solubilize free pyrene, 1 or 10% (v/v) dimethyl sulfoxide was added as cosolvent for several runs. Detailed binding studies in binary solvent mixtures of various compositions have shown that the addition of 1 or 10% dimethyl sulfoxide does not dramatically change the complexation properties of a pure solvent like water or *N*,*N*-dimethylformamide. Rather, free energies of apolar complexation in binary solvent mixtures of various composition give linear free energy relationships ($R \geq 0.99$) with the $E_T(30)$ values of the mixtures.[14,21] Figure 1 shows the linear free energy relationship between the free energies of formation of complex **1** in 18 solvents and the solvent polarity parameter $E_T(30)$.

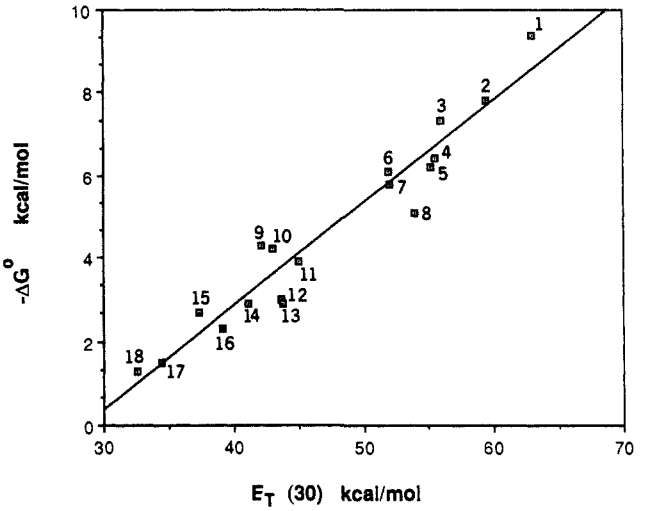

Figure 1. Dependence of the free energy of formation $-\Delta G°$ (kcal·mol^{-1}) of complex **1** (T = 303 K) on the solvent polarity as expressed by $E_T(30)$ values (kcal·mol^{-1}).[20a] The numbers in the graph refer to the entries shown in Table I.

The following conclusions are drawn from the data in Table I and Figure 1:

(i) Linear Gibbs free energy correlations using $E_T(30)$ values have been successfully applied for predicting solvent effects on reaction rates, reaction equilibria, solute–solvent interactions, and

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(21) The free energy of complexation of neutral benzene derivatives by cyclophanes with apolar binding sites correlates extremely well ($R \geq 0.99$) with the $E_T(30)$ values in the binary solvent mixtures water–methanol and water–dimethyl sulfoxide (Sanford, E. M.; Diederich, F., unpublished results).

spectral absorptions.[20a] The $E_T(30)$ values reflect all the nonspecific intermolecular forces between solvent and solute molecules occurring in these processes. Macroscopic solvent properties such as dielectric constant, dipole moment, refractive index, cohesion, and polarizability have been found to be related by $E_T(30)$ parameters.[20b,c] Figure 1 shows that this empirical solvent polarity parameter is also very useful for predicting the strength of apolar host–guest complexation in solvents of all polarities. The correlation coefficient for the linear free energy relationship shown is $R = 0.934$. This correlation allows predictions for the binding energies of complex **1** in additional solvents according to the equation $-\Delta G° = 0.25E_T - 7.1$ (kcal·mol^{-1}). Linear correlations of similar significance are also obtained, when the stability of the perylene and fluoranthene complexes in various solvents[13] are plotted against $E_T(30)$ values.

(ii) The impact of solvation effects on complexation strength is impressive. Upon changing from the most polar solvent, water, to the least polar solvent considered in this study, carbon disulfide, complexation free energies decrease from $-\Delta G° = 9.4$ kcal·mol^{-1} to $-\Delta G° = 1.3$ kcal·mol^{-1}.

(iii) The linear free energy relationship also holds for water. Binding strength decreases regularly from water to polar protic solvents to dipolar aprotic and to apolar solvents. We conclude that water does not promote apolar complexation beyond the level expected on the basis of its physical properties such as dielectric constant, polarizability, or dipole moment expressed in the empirical solvent polarity parameter.

(iv) Of great interest is the finding that some of the new solvents investigated in this study approach water in their potential for promoting apolar complexation. This also strongly supports that the magnitude of apolar binding in water does not need a special explanation.[18] Very strong complexation is observed in 2,2,2-trifluoroethanol (run 2) and in ethylene glycol (run 3). The complex stability in these solvents is higher than in methanol (run 4). The amide solvents demonstrate diverse properties. While the complexation strength in formamide (run 5) is comparable to those in methanol and ethanol (run 6), binding in the N-alkylated amides (runs 7, 8, 10, and 12) becomes increasingly unfavorable.

The observation that very stable complexes of apolar solutes can form in solvents other than water opens new perspectives for supramolecular recognition and catalysis. Stable molecular complexes can be formed in solvents like 2,2,2-trifluoroethanol, ethylene glycol, methanol, or formamide in which many apolar substrates are more soluble than in water. These solvents could provide a better environment than water for growing crystals of cyclophane complexes suitable for X-ray analysis. The growth of quality crystals from aqueous solutions has not been very successful in the past.[1-12] In nonaqueous solvents, the rates of catalytic processes in supramolecular complexes and the selectivity with regard to reaction, substrate, and stereochemistry will be different than those in water. Acid–base catalysis and the solvation of ground states and transition states will be considerably altered in these solvents as compared to water.

Several recent studies have demonstrated apolar binding phenomena that correlate with solvent polarity similar to the correlation we report for the solvent-dependent stability of complex **1**. Breslow and Gao have shown that the Diels–Alder reaction, which involves the tight packing of apolar surfaces in the reaction transition state, is faster in organic solvents which also give complex **1** greater stability.[22] The rates of Diels–Alder reactions of nitrosobenzene with 1,3-cyclohexadiene and of methyl vinyl ketone with 1,3-cyclopentadiene are fastest in water as solvent, and the rates in formamide and in ethylene glycol are larger than in other organic solvents. Formamide and ethylene glycol also promote the Diels–Alder reaction catalyzed by β-cyclodextrin since these solvents favor the stabilization of the hydrophobic reaction transition state in the apolar cyclodextrin cavity. We predict that 2,2,2-trifluoroethanol should be second to water in promoting the Diels–Alder reaction.

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Recent work by Klibanov et al. shows that enzymes in organic solvents have exciting properties that differ significantly from those known to occur in aqueous solutions.[23] Dramatic changes in reaction selectivity and stereoselectivity have been observed in several studies. In one example, changes in enzyme enantioselectivity as a function of reaction medium could be predicted and rationalized by a linear free energy relationship which included dipolar aprotic and apolar solvents.[23c] Enzyme enantioselectivity was explained by differences in hydrophobic substrate binding and was also found to correlate with solvent polarity analogously to the way the stability of complex **1** is dependent upon solvent polarity.

Origin of the Large Solvent Dependency of Apolar Complexation: A General Model for Solvation

The attractive host–guest interactions that stabilize complex **1** with its very tight geometric complementarity are London dispersion interactions and local dipole-induced dipole interactions. Since the geometry of complex **1** in all 18 solvents is very similar, a large difference in attractive host–guest interactions in the various environments cannot be the origin of the observed changes in binding strength. Hence, the difference in free binding energy of $\Delta(\Delta G°) = 8.1$ kcal·mol^{-1} observed upon changing from water to carbon disulfide is predominantly due to solvation phenomena. Since solvation alters complexation strength in a rational way as suggested by a valid linear free energy relationship, we propose a general model for solvation effects on apolar binding.

Whether a solvent promotes or inhibits apolar complexation depends on how favorable it is for the solvent to solvate the complementary apolar surfaces of the free binding partners. If the solvation of the apolar binding partners is favorable, the overall driving force for molecular complexation will be weak. Strong complexation occurs in solvents that do not solvate favorably the complementary apolar host and guest surfaces. We identify two solvent properties, cohesive interactions and polarizability, as the major factors controlling apolar binding strength.[16]

Role of Solvent Cohesive Interactions. Solvation of the free binding partners is enthalpically unfavorable if the solvent molecules have strong cohesive interactions. High cohesive interactions make it more favorable for solvent molecules to interact with themselves than to solvate apolar surfaces and especially deep apolar cavities.

The *cohesive pressure* c measures the total molecular cohesion per unit volume of solvent and is defined by eq 1,[24] where ΔU_{vap}

$$c = \frac{\Delta U_{vap}}{V_m} = \frac{\Delta H_{vap} - RT}{V_m} \quad \text{(MPa)} \tag{1}$$

$$\delta = c^{1/2} \quad \text{(MPa}^{1/2}\text{)} \tag{2}$$

and ΔH_{vap} are respectively the energy and enthalpy (heat) of vaporization of the solvent to a gas of zero pressure and V_m is the molar volume of the solvent. Upon vaporization of a solvent to a noninteracting vapor, all intermolecular solvent–solvent interactions will be broken. Cohesive pressure is related to the energy required to create cavities in a liquid in order to accommodate solute molecules, e.g., pyrene, during the process of dissolution. Such cavities are also created when solvent molecules enter the free host cavity upon solvation. In comparing solvents, those having larger c values exhibit greater cohesive interactions, and therefore, cavity formation is less favorable. The solubility parameter δ (MPa$^{1/2}$) by Hildebrand and Scott[25] is defined as the square root of the cohesive pressure c of solvents. Figure 2 shows the free energy of formation of **1** plotted as a function of δ.[26] The

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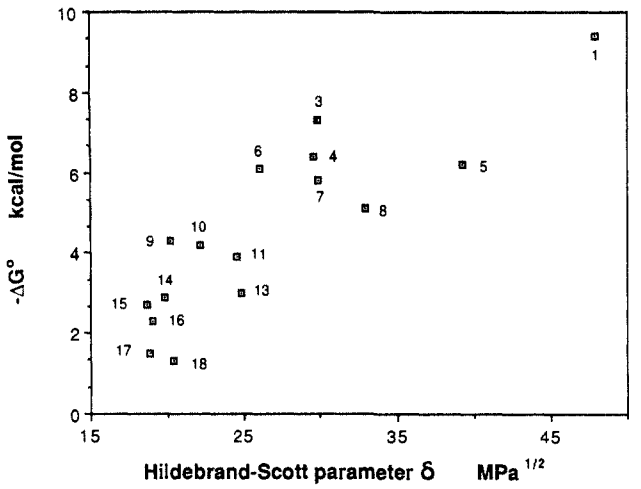

Figure 2. Free energy of formation $-\Delta G°$ (kcal·mol^{-1}) of complex **1** plotted against the Hildebrand–Scott parameter δ (MPa$^{1/2}$)[25,26] which measures solvent cohesive interactions. The numbers in the graph refer to the entries shown in Table I. The Hildebrand–Scott parameters of the pure solvents are plotted and have not been corrected for the addition of 1 or 10% (v/v) Me_2SO as a cosolvent in several runs.

solvent cohesive interactions decrease from water to nonaqueous polar protic solvents, to dipolar aprotic solvents, and finally to apolar solvents, the same sequence which is observed for the stability of complex **1**. Obviously, the correlation of the binding data with δ is not as good as their correlation with E_T since solvent cohesive interactions represent only one of the major solvent properties that reflect solvation effects. However, a clear trend is visible in Figure 2; apolar binding strength increases with increasing solvent cohesive interactions. We note that similar viewpoints related to the energy requirements for cavity formation in a solvent had been promoted by Sinanoglu to explain strong apolar binding in water.[27]

Water and the nonaqueous polar protic solvents, e.g., ethylene glycol, methanol, and formamide (runs 1–8 in Figure 2), are the best solvents for apolar binding. They are characterized by strong cohesive interactions resulting from hydrogen-bonding networks.[15a-c,28] Solvent molecules that solvate the deep host cavity and possibly also those solvating the free guest have reduced hydrogen-bonding interactions. Such molecules are enthalpically higher in energy than the solvent molecules in the bulk. They participate in fewer strong hydrogen bonds than those in the bulk. Upon inclusion complexation, these solvent molecules are released into the bulk and become enthalpically lower in energy.

Strong solvent cohesive interactions such as hydrogen-bonding networks lead to the formation of ordered solvent cages around apolar solutes.[15a-c] These ordered solvent cages allow solvating molecules to maintain the best possible interactions with themselves and with other solvent molecules in the bulk. Upon complexation, these solvent cages around the complementary surfaces of host and guest break down, and the solvent molecules are released into the bulk which represents a less ordered state. This process is characterized by a positive entropy term and, for aqueous solutions, is known as the classical entropic hydrophobic effect.[15]

For a series of solvents of similar shapes, in which the number of molecules composing the solvation shells of the complementary host and guest surfaces is not very different, the molar heat of vaporization ΔH_{vap} (kcal·mol^{-1}; eq 1) appears to be a good measure for the cohesive interactions. Figure 3 shows a very good correlation (R = 0.967) between the stability of complex **1** and the molar heat of vaporization of various alkylated formamides and

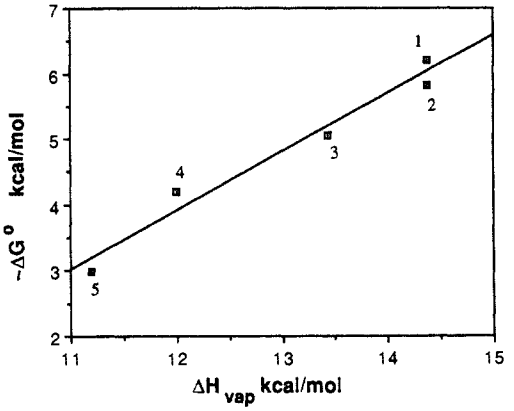

Figure 3. Dependence of the free energy of formation $-\Delta G°$ (kcal·mol^{-1}) of complex **1** on the molar heat of vaporization ΔH_{vap} of the solvents formamide (1), *N*-methylacetamide (2), *N*-methylformamide (3), *N*,*N*-dimethylacetamide (4), and *N*,*N*-dimethylformamide (5). The $-\Delta G°$ values are measured in solvents containing 10% (v/v) dimethyl sulfoxide and are taken from Table I.

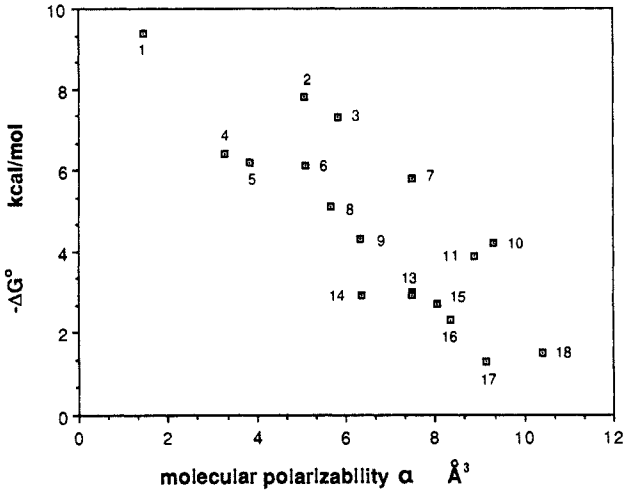

Figure 4. Free energy of formation $-\Delta G°$ (kcal·mol^{-1}) of complex **1** plotted against the molecular polarizabilities α (Å^3) which measure the potential of the solvent molecules for London dispersion interactions. The numbers in the graph refer to the entries shown in Table I. The molecular polarizabilities of the pure solvents are plotted and have not been corrected for the addition of 1 or 10% (v/v) Me_2SO as a cosolvent in several runs.

acetamides.[29] Complexation is strongest in those solvents capable of forming the strongest hydrogen-bonding networks. This adds further support to the important role that solvent cohesive interactions play in determining whether a solvent promotes or inhibits apolar complexation.

Role of London Dispersion Interactions.[15d,30a] The attractive B term in the $Ar^{-12} - Br^{-6}$ Lennard-Jones potential to define London dispersion interactions is proportional to the polarizability α (Å^3) of the interacting atoms. Oxygen atoms (α = 0.84 Å^3) and hydroxyl residues (α = 1.20 Å^3), the constituents of water and hydroxylic solvents, have low polarizabilities whereas organic residues, e.g., an aliphatic CH_2 (α = 1.77 Å^3), a methyl group (α = 2.17 Å^3), or an aromatic CH group (α = 2.07 Å^3), have much higher polarizabilities.[30] For evaluating the dispersion interaction potential of organic solvents, we have chosen the molecular polarizabilities of the solvents. These were either determined experimentally or calculated from atomic increments.[31] Figure 4 shows the free energy of formation of **1** plotted against

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(28) (a) Reference 20a, Chapter 2.2.5, pp 13–17. (b) For hydrogen-bonding networks in liquid formamide and *N*-methylformamide, see: Ohtaki, H.; Funaki, A.; Rode, B. M.; Reibnegger, G. J. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2116–2121; Ohtaki, H.; Itoh, S.; Rode, B. M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 271–276.
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the molecular polarizabilities of the solvents. Water possesses by far the lowest polarizability (α = 1.47 Å^3). With increasing solvent polarizability, the complexation of pyrene (α = 29.34 Å^3)[31] becomes increasingly weaker. In a weakly polarizable solvent, the dispersion interactions between solvent molecules and the complementary apolar surfaces of host and guest are weaker than the forces between the two highly polarizable hydrocarbon surfaces in the complex. Upon complexation, the less favorable contacts between the solvent molecules and the hydrocarbon surfaces are replaced by the more favorable close contacts between the complementary surfaces of the binding partners. This generates a favorable enthalpic component of the complexation process. During complexation in highly polarizable solvents, favorable solvent–solute dispersion interactions are replaced by host–guest interactions of similar energy. In such solvents, there is little or no driving force due to dispersion interactions.

Apolar complexation seems to be favored in solvents characterized by high cohesive interactions and low molecular polarizability. It is obvious that the plots in Figures 2 and 4 show general valid trends rather than good correlations. Only the empirical solvent polarity parameter $E_T(30)$, which reflects the combination of solvent properties including *both* cohesive interactions and polarizability, shows a very good correlation. The fine correlation of free binding energies with E_T values is, at first, surprising in view of the different fit of the various solvent molecules into the host cavity.[32] According to CPK model examinations, more than ten water molecules, approximately six methanol molecules, two *N*,*N*-dimethylacetamide, or two benzene molecules can readily solvate the highly preorganized binding site of the free macrobicyclic host. The $E_T(30)$ parameter, which measures the energy of the longest wavelength electronic transition of the large betaine dye 2,6-diphenyl-4-(2,4,6-triphenyl-1-pyridinio)phenoxide, obviously also considers the fact that more of the small water or methanol molecules than of the larger *N*,*N*-dimethylacetamide or benzene molecules are needed to solvate a given apolar surface area.

In Conclusion, we have studied the stability of complex **1** in a total of 18 solvents including water. For the first time, apolar complexation has been compared in water and in organic solvents chosen over the entire polarity scale. Complexation strength decreases steadily from water ($-\Delta G°$ = 9.4 kcal·mol^{-1}) to nonaqueous polar protic solvents, to dipolar aprotic solvents, and to apolar solvents like carbon disulfide ($-\Delta G°$ = 1.3 kcal·mol^{-1}). The large difference in binding strength results almost exclusively from solvation effects. A linear free energy relationship is valid between the free energies of complexation and the empirical solvent polarity parameters $E_T(30)$ for the various solvents. With 2,2,2-trifluoroethanol, a solvent has been explored which comes close to water in its ability to promote apolar complexation. Strong complexation is also observed in ethylene glycol and in formamide. A general model for solvation effects on apolar complexation is presented. This model describes which *macroscopic* solvent properties appear to be most important in determining the strength of apolar host–guest complexation. Binding is strongest in solvents characterized by low molecular polarizabilities and by high cohesive interactions. Solvent molecules with high cohesive interactions interact more favorably with bulk solvent molecules than with the complementary apolar surfaces of free host and guest, and therefore, energy is gained upon the release of surface-solvating molecules to the bulk during the complexation step. Upon complexation, the less favorable dispersion interactions between solvent molecules of low polarizability and highly polarizable hydrocarbon surfaces are replaced with more favorable dispersion interactions between the complementary surfaces of host and guest. No special concepts are needed to explain the great ability of water to promote apolar complexation. The solvation properties of water can be rationalized on the basis of its physical properties.[33] Water has the highest cohesive interactions and possesses by far the lowest molecular polarizability. *Both effects taken together* make it the best solvent for apolar complexation. The present study demonstrates that the entire solvent polarity range needs to be explored to understand the role water or any organic solvent has in a molecular recognition process. Future comparative calorimetric and computational studies will enable the enthalpic and entropic contributions to the free energy of binding in aqueous and organic solvents to be determined and a complete thermodynamic cycle for apolar host–guest complexation to be defined.

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Experimental Section

General. Solvents of purity greater than 99% were purchased from Aldrich, and optical purity was tested prior to use in fluorescence titrations. The deuterated solvents with highest degree of deuteration were purchased from either Aldrich or MSD isotopes. Pyrene was recrystallized twice from ethanol, sublimed, and further purified by zone melting. The preparation of the cyclophane host is described in ref 13. Fluorescence titrations were obtained on a SPEX 212 fluorolog. ^{1}H NMR spectra were obtained on a Bruker HX 360 instrument. The association constants for runs 4, 6, 9, 11, 13, and 15–18 in Table I had been determined in previous work.[13] Experimental details for the latest binding studies yielding the important data for water, 2,2,2-trifluoroethanol, ethylene glycol, dichloromethane, and the series of alkylated formamides and acetamides are described below. The $E_T(30)$ parameters for the solvent mixtures containing dimethyl sulfoxide as added cosolvent were determined from a Varian Cary 2300 spectrometer. The longest absorption wavelength of the betaine dye 2,6-diphenyl-4-(2,4,6-triphenyl-1-pyridinio)phenoxide was measured for each solvent and converted to E_T (kcal·mol^{-1}) with the relationship $E_T = (2.859 \times 10^{-3})\nu$ (cm^{-1}).[20a]

Fluorescence Titrations. The run solutions consisted of nine sequential dilutions from a host stock solution and an aliquot from a guest stock solution. The run solutions were pipeted into a 1-cm quartz cuvette. The cuvette was placed in the thermostated cell holder and was allowed to reach an equilibrium temperature of T = 303 ± 0.3 K. This took approximately 15 min, and the temperature was measured with a digital microthermometer. The fluorescence intensity of pyrene for each point of a titration curve was measured by scanning a particular emission wavelength approximately 10 times with a 3-s integration time and taking the average of the intensities. The wavelength of excitation was λ_{exc} = 341 nm where strong absorption of complexed pyrene occurs. The observed emission wavelength was λ_{em} = 394 nm. The equilibrium constants for host–guest complexation were derived from a nonlinear least-square curve fitting procedure. At the end points of the titrations, approximately 80–90% of the emission intensity at saturation binding was observed. The K_a values obtained in triplicate runs were in good agreement, and the given K_a value is their average.

Since concentration ranges for titrations provide valuable information on the significance of measured association constants, the concentration ranges in fluorescence titrations are given. (a) In H_2O/Me_2SO (99:1 v/v), [Na_2CO_3] = 10^{-3} mol·L^{-1}, [host] = 1.0×10^{-7} to 1.0×10^{-6} mol·L^{-1}, and [pyrene] = 5.0×10^{-8} mol·L^{-1}. (b) In 2,2,2-trifluoroethanol/Me_2SO (99:1 v/v), [host] = 1.6×10^{-6} to 2.8×10^{-5} mol·L^{-1}, and [pyrene] = 8.5×10^{-7} mol·L^{-1}. (c) In ethylene glycol/Me_2SO (90:10 v/v), [host] = 5.5×10^{-6} to 6.5×10^{-5} mol·L^{-1}, and [pyrene] = 9.2×10^{-6} mol·L^{-1}. (d) In formamide/Me_2SO (90:10 v/v), [host] = 1.0×10^{-5} to 1.0×10^{-4} mol·L^{-1}, and [pyrene] = 1.0×10^{-5} mol·L^{-1}. (e) In *N*-methylacetamide/Me_2SO (90:10 v/v), [host] = 1.0×10^{-5} to 1.0×10^{-4} mol·L^{-1}, and [pyrene] = 1.0×10^{-5} mol·L^{-1}. (f) In *N*-methylformamide/Me_2SO (90:10 v/v), [host] = 1.0×10^{-4} to 1.0×10^{-3} mol·L^{-1}, and [pyrene] = 1.0×10^{-5} mol·L^{-1}.

^{1}H NMR Titrations. All ^{1}H NMR titrations were run at T = 303 ± 1 K, and the complexation shifts of all three resonances of pyrene as a function of host concentration were evaluated in binding titrations as discussed above. The final K_a values are averages of the values obtained in the evaluation of the three individual protons. Concentration ranges for the NMR titrations are as follows: (a) In *N*,*N*-dimethylacetamide/Me_2SO-d_6 (90:10 v/v), [host] = 1.5×10^{-3} to 1.5×10^{-2} mol·L^{-1}, and [pyrene] = 5.0×10^{-3} mol·L^{-1}; 90% of saturation binding was observed. (b) In *N*,*N*-dimethylformamide-d_7/Me_2SO-d_6 (90:10 v/v), [host] = 1.5×10^{-3} to 1.5×10^{-2} mol·L^{-1}, and [pyrene] = 5.0×10^{-3} mol·L^{-1}; 62% of saturation binding was observed. (c) In CD_2Cl_2, [host] = 6.6×10^{-4} to 8.2×10^{-3} mol·L^{-1}, and [pyrene] = 9.4×10^{-4} mol·L^{-1}; 50% of saturation binding was observed. For a detailed discussion of the complexation shifts observed upon formation of **1**, which support the complex structure shown, see ref 13.

Acknowledgment. This work was supported by the Office of Naval Research and the National Science Foundation.